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Synthesis of a Potential Antiviral Compound: 5-Bromoethynyl-2'-deoxyuridine

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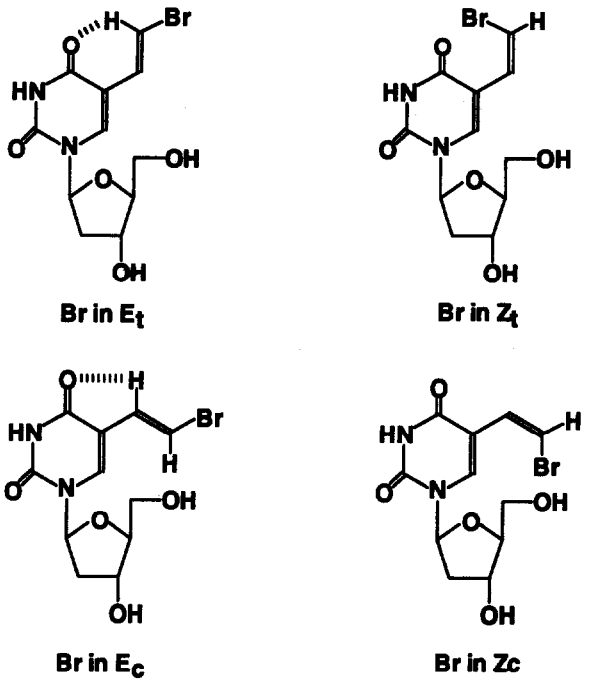
Abstract: 5-Bromoethynyluracil and its deoxyriboside can be prepared in good yields starting from dibromovinyluracil, which is accesible by literature methods. 5-Bromoethynyl-deoxyuridine is less effective against HSV-1 than *E*-(bromovinyl)-deoxyuridine but, similar to BVDU, seems to exhibit a certain selectivity toward HSV-1. Molecular calculations prove the spatial similarity of both compounds.

INTRODUCTION

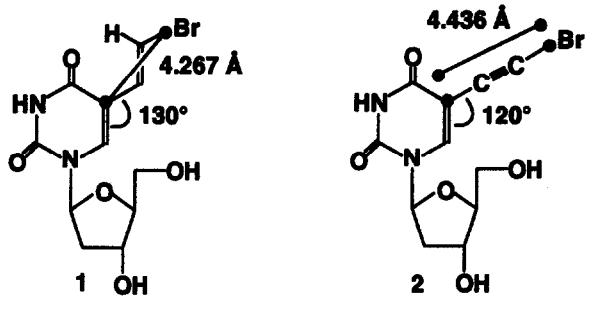
The antiviral compound bromovinyldeoxyuridine (BVDU, **1**) is known to be one of the most active pyrimidine nucleosides[1] against herpes simplex virus type 1 (HSV-1). The active form of BVDU is known to be the *E*-configurated drug, which, with respect to the position of the halogen atom, can exist either in the transoid structure E_t or as the cisoid isomer E_c (scheme 1).

Following E. De Clercq[2] only the E_t isomer possesses the optimal geometry to activate viral thymidine kinase (TK) of HSV-1. Rotating the side chain by only one single bond transforms E_t into E_c, which is said to be inhibited by the stabilization of E_t via a hydrogen bond between O-4 of the pyrimidine ring and the hydrogen at C-2 of the side chain. The possibility of this H-bond is confirmed by X-ray analyses.[3] From the small differences in electronegativity between carbon and hydrogen a very poor polarization of the C-H bond in the side chain results, so the importance of the proposed H-bond should not be overemphasized. Especially in aqueous solution the influence of the solvent has to be taken into account. Furthermore, according to modelling studies the E_c-rotamer could also be stabilized by a hydrogen bond starting from C-1 of the side chain (scheme 1).



Scheme 1: Possible configurations and conformations of BVDU (1)

In contrast to *E*-BVDU, the new potential antiviral 5-bromoethynyl-deoxyuridine (2) does not show E/Z-isomerism. A calculation of geometry optimization and energy minimization reveals that in both compounds the volumina of the side chains and the relative positions of the halogen atoms are comparable: in 1 the distance between C-5 and Br is 4.267 Å, and the bond angle C-6/C-5/C-1' is 130° (scheme 2). In 2 the same distance is calculated to 4.436 Å and the corresponding angle to 120°.



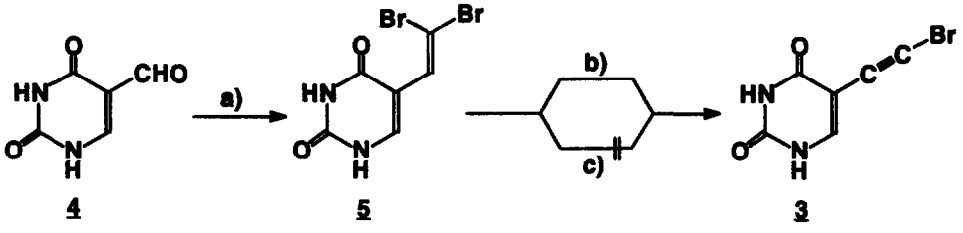
Scheme 2: Computer calculated bond angles and distances in 1 and 2

According to our testing, **2** also is an active compound against HSV-1, which may be explained by the spatial similarity of **1** and **2**, and which would suggest that the stabilization of **1** via an H-bond cannot be the only explication of the action mechanism of BVDU. In 1981 Barr and Walker published an unsuccessful attempt to prepare **2**.[4] We are now able to present a reproducible and efficient way to obtain **2**.

SYNTHESIS OF 5-(BROMOETHYNYL)-URACIL

5-(Bromoethynyl)-uracil (**3**) was first synthezised by Barr et al. in moderate yields[4a, 5] from 5-(1-chloro-2-bromovinyl)-uracil. As the yield was not satisfactory for our purposes, we attempted to prepare **3** starting from 5-(2,2-dibromovinyl)-uracil (**5**): 5-formyl-uracil[6] (**4**) was transformed into **5** by the Wittig reaction, using the procedure of Schroeder et al.[7]

Attempts to eliminate HBr by the application of n-butyllithium at -78°C yielded 5-ethynyl-uracil.[8] In 1989 Buckle and Finwick[9] described the elimination of HBr from β,β-dibromo-2-(oct-1-ynyl)-styrene with potassium-tert.-pentoxide in n-hexane. The insolubility of **5** in n-hexane and the commercial inaccesability of potassium-tert.-pentoxide forced us to modify this procedure. Substituting potassium-tert.-pentoxide by potassium-tert.-butoxide only led to a decomposition of the reaction mixture. The selective elimination of only one bromo atom from **5** finally was realized with the aid of sodium-tert.-pentoxide in DMF at -10°C (scheme 3).



4 **5** **3**

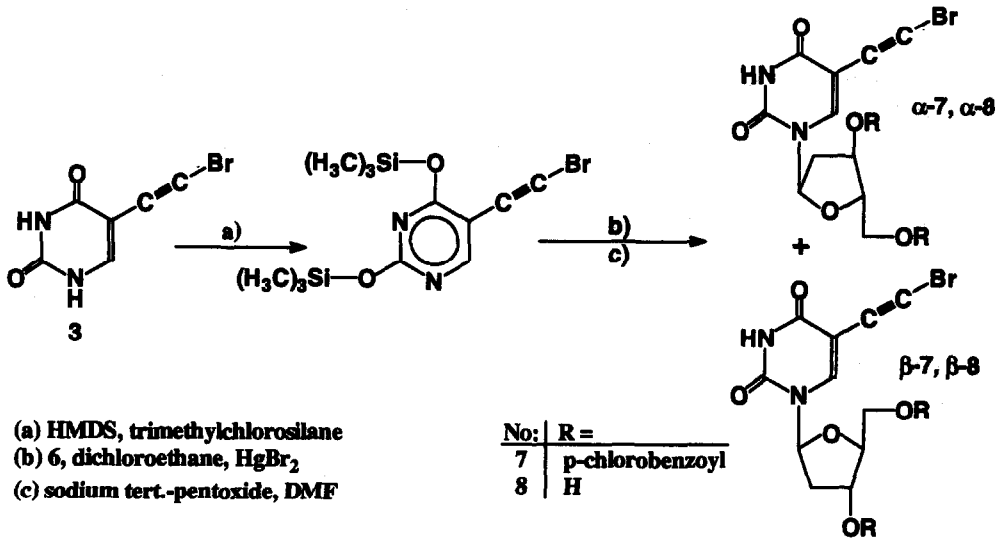
a) see lit. 7)
b) sodium-tert.-pentoxide, DMF, -10°C
b) potassium-tert.-butoxide

Scheme 3: Preparation of 5-(bromoethynyl)-uracil (**3**)

SYNTHESIS OF 5-(BROMOETHYNYL)-DEOXYURIDINE

In the classical Hilbert-Johnson procedure for the formation of nucleosides, silylated pyrimidines are treated with protected α-halogeno sugars in the presence of catalytic amounts of $AgClO_4$, $HgBr_2$ or Lewis acids.[10] To prevent side reactions, the OH group in C-3' and C-5' of the deoxyribose moiety must be protected. Usually for this purpose a p-toluoyl group is used,[11] because the resulting 2-deoxy-3,5-di-O-(p-toluoyl)-D-ribofuranosyl chloride is a good reactant and is stable against acids. But as this protected sugar is oily, its purification is tedious. Instead we used 2-deoxy-3,5-di-O-(p-chlorobenzoyl)-D-ribofuranosyl chloride (**6**), a readily crystallizing compound.

The silylation of **3** is achieved by reacting the substance in hexamethylene disilazane (HMDS) with catalytic amounts of trimethylchlorosilane according to the procedure of Wittenburg.[12] The silylated heterocycle was treated with the halogenated sugar (**6**) in dichloroethane with $HgBr_2$ as a catalyst (scheme 4). Lewis acids such as $SnCl_4$ proved to be not suitable in this reaction. The resulting protected α- and β-nucleosides **7** were purified by column chromatography.



Scheme 4: Preparation of 5-(bromoethynyl)-2'-deoxyuridine (**8**)

DISCUSSION

Preparing nucleosides one has to determine whether the product is an α/β-ribofuranoside or an α/β-ribopyranoside. A fifth possible form, the open chain isomer, can easily be excluded by microelemental analysis, because the product should then have a molecular mass that exceeds the mass of the pyranoid/furanoid form by 18.

Distinguishing between a pyranose and a furanose can be done by nmr spectroscopy: the isomers differ in their chemical shifts[13] and in their coupling constants.[14] In the ^1H nmr spectra the resonance of H-1' of a pyranose appears upfield with respect to a furanose. Chemical shifts of H-3' and H-4' in a furanose usually differ by more than 0.5 ppm,[15] whereas in a pyranose both signals appear superimposed. With these findings in mind, our nucleoside can be recognized as a ribofuranoside.

Differentiation between α- and β-ribofuranosidic nucleosides is possible by comparing the chemical shifts and coupling constants of the sugar protons. In α-isomers H-1' appears as a doublet, whereas in β-compounds the same atom shows resonance as a triplet.[16] The width of the multiplet of H-2' in α-isomers[17] usually is much larger (>1 ppm) than in β-nucleosides (<0.7 ppm). In addition the chemical shift of H-4' is a good indicator for the configuration of nucleosides:[15] H-4' in α appears downfield with respect to β-nucleosides.

Our nmr findings allow us to unambiguously assign the α- and β-configuration to **7** and **8**: H-1' in **α-7** appears as a doublet, whereas in **β-7** it shows resonance as a triplet. H-4' in **α-7** gives rise to a doublet at 5.2 ppm, in **β-7** it is shifted upfield to the typical value of 4.55 ppm.

After deprotection of the sugar (scheme 4, **8**) the aromatic signals of the p-chlorotoluoyl group dissapear, whereas the exchangeable OH groups appear near 5.1 ppm. The ethynyl moiety can easily be identified via ir spectroscopy by a typical peak at 2207 cm^{-1}.

BIOLOGICAL TESTING

5-(Bromoethynyl)-deoxyuridine (**2**) and its synthetical precursors were evaluated for their cytotoxicity and tested for their antiviral effects against HSV-1 and HSV-2, using *E*-BVDU (**1**) as a reference (tables 1 - 2). **1** was found to act more selective against HSV-1 than against HSV-2, which is confirmed in our experiment. In contrast, **2** did not show this selectivity, though the effect against HSV-1 was somewhat stronger. Compunds **3**, **4**, and **5** were not expected to act as antivirals, so the negative results were not dissapointing. In a concentration of 500 µg/ml **2** and **5** were cytotoxic.

Table 1: In Vitro Antiviral Activity against HSV-1/HSV-2

Compound	0.5 µg/ml [%]	5 µg/ml [%]	50 µg/ml [%]	500 µg/ml [%]
1	100/0	100/0	100/75	100/100
2	0/0	75/50	100/75	(-)
3	0/0	0/0	0/0	0/0
4	0/0	0/0	0/0	25/0
5	0/0	0/0	0/0	(-)

(-) cytotoxicity predominates antiviral activity

Table 2: In Vitro Cytotoxicity

Compound	0.5 µg/ml [%]	5 µg/ml [%]	50 µg/ml [%]	500 µg/ml [%]
1	0	0	0	0
2	0	0	0	100
4	0	0	0	25
5	0	0	25	100

EXPERIMENTAL SECTION

1. Computer Modelling

Molecular modelling was done on a MicroVAX 3500 with a PS390 graphical output system. For geometry optimizing Sybyl Modelling Software 5.4, Tripos Ass. Inc., St. Louis, Mo., USA was used, calculations of electrostatic fields were done with MOPAC 5.0, QCPE #455.

2. Biological Methods

The compounds were added to mice embryo cell cultures in concentrations of 0.5, 5, 50, and 500 μg/ml and incubated for 3 days. Subsequently the cell plaques were controlled macro- and microscopically. Growth inhibition or disruption of noninfected cells indicated cytotoxicity. As a parameter for antiviral effects the reduction or inhibition of cell destruction of HSV-1 infected plaque assays was used. *E*-BVDU was used as a reference.

3. Synthesis

Melting points were determined on a Büchi 510 melting point apparatus, and are uncorrected. The ir spectra (potassium bromide) were recorded on a Perkin Elmer 1750 FTIR spectrometer. The ^{1}H and ^{13}C nmr spectra were measured on a Bruker AC80 spectrometer using tetramethylsilane as an internal standard. For the resonance signals the following abbreviations are used: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet; br, broad. In all cases the solvent was [d6]-DMSO. The structural assignment derived from the spectra was confirmed by comparison to literature data. Mass spectra were obtained on a Finnigen MAT 711A spectrometer (modified by AMD Intectra GmbH) using a direct inlet system. They were recorded by the Abteilung Massenspektroskopie, Organisch-Chemisches Institut der Universität Tübingen. Elemental Analysis was performed by the Abteilung Elementaranalyse, Anorganisch-Chemisches Institut der Universität Tübingen.

Solvents for the reaction of silylated pyrimidines with protected sugars were carefully purified. 1,2-Dichloroethane was refluxed with phosphorus-(V) oxide for two hours, distilled and stored on molecular sieve (4Å). Dimethyl formamide was refluxed with calcium hydride for 8 hours and then fractionated in vacuo. Pyridine was refluxed with solid potassium hydroxide (100g/l) and then fractionated on a 20 cm Vigreux column at normal pressure (114 - 115°C). Dichloromethane was refluxed with phosphorus-(V) oxide (20g/l) and then distilled.

5-Formyl-uracil (**4**)[6] and its precursor 5-(2-hydroxyethyl)-uracil[18] were prepared from uracil by literature procedures. Commercially available chemicals were purchased from E. Merck, Fluka, and Aldrich Chemie, Germany.

2-Deoxy-3,5-di-O-(p-chlorobenzoyl)-D-ribofuranosyl chloride (6)

8.4 g (62 mmol) deoxy-D-ribose were dissolved in 160 ml of absolute methanol. 8.4 ml of 1% methanolic HCl were added and the mixture was stirred at room temperature. After 45 min the solution was neutralized with 42 ml of abs. pyridine and the solvent was removed in vacuo. In order to purify the oily product from traces of methanol, 20 ml of dry pyridine were added to the residue and the solvent was again evaporated. The oily sugar was dissolved in 50 ml of abs. pyridine. Under cooling and exclusion of moisture 20 ml of p-chlorobenzoyl chloride were added. The internal temperature must not exceed 30°C. The reaction mixture was stirred at room temperature overnight. The precipitate was filtered off, dissolved in 20 ml of dichloromethane and the excess of p-chlorobenzoyl chloride was hydrolized with 125 ml of water. The aqueous layer was reextracted with 60 ml of dichloromethane. The combined organic fractions were washed twice with each 120 ml of a cold, saturated solution of $NaHCO_3$, water, cold 3N H_2SO_4 and again with water. After drying with Na_2SO_4 the solvent was removed in vacuo.

The oily residue was dissolved in 30 ml of absolute toluene and evaporated in vacuo in order to remove traces of water as an azeotrope. The product was then dissolved in 36 ml of toluene and stored at 0°C for 1 h. The precipitate was filtered off and washed with toluene. The combined filtrates were concentrated to a syrup and then dissolved in 48 ml of glacial acetic acid. After addition of 90 ml of a cold saturated solution of dry HCl in abs. acetic acid under cooling in an ice bath the product precipitated from the solution. The precipitation was completed after 20 min. The product was filtered off and washed with abs. ether until the filtrate was neutral. **6** was dried over KOH in vacuo (>1 mbar). Yield: 20.2 g (76%). Mp.: 125 - 126°C. Anal. Calcd for $C_{19}H_{15}O_5Cl_3$ (429.6): C, 53.11; H, 3.49; Cl 24.78. Found: C, 53.21; H, 3.51; Cl, 25.02. ^{1}H-nmr (δ [ppm]): 2.75 - 2.87 (m, 2H, H-2,2'), 4.65 (m, 2H, H-5,5'), 4.85 (m, 1H, H-4), 5.53 (m, 1H, H-3), 6.40 (dd, 1H, H-1), 7.25 - 8.10 (2x m, 2x 4H, 2x p-chlorobenzoyl).

5-Formyluracil (4)

3.1 g (20 mmol) of hydroxyethyluracil,[18] 0.1 g of silver nitrate and 10.8 g of potassium persulphate were dissolved in 100 ml of water and stirred at 30 - 40°C. After 3 hrs the precipitate was collected by filtration and washed neutral with ice cold water. Yield: 1.42 g (51%). Mp.: >290°C (dec.). Anal. calcd. for $C_5H_4N_2O_3$ (140.0): C, 42.86; H, 2.88; N, 20.00. Found: C, 41.96; H, 2.83; N, 20.20. IR (cm^{-1}): 1724 (CHO), 1706 - 1670 (lactam). ^{1}H-nmr (δ [ppm]): 8.13 (s, 1H, H-6), 9.74 (s, 1H, CHO), 11.74, 11.83 (2x s, 2x 1H, 2x NH).

5-(2,2-Dibromovinyl)-uracil (5)

5.25 g (20 mmol) of triphenylphosphine, 6.6 g (19.9 mmol) of carbon tetrabromide and 1.3 g (19.9 mmol) of zinc dust were reacted in 50 ml of abs. dichloromethane at room temperature under an argon atmosphere. After 24 hrs of stirring, 1.4 g (10 mmol) of **4**, dissolved in 10 ml of abs. DMF were added and stirred for additional 24 hrs. The precipitate was filtered off, washed with chloroform several times, and recrystallized from methanol. In order to increase the yield the filtrate was evaporated in vacuo and the residue was suspended in chloroform. The precipitate was filtered off and recrystallized from methanol. Yield: 1.9 g (65%). Mp.: 280 - 282°C. Anal. calcd. for $C_6H_4Br_2N_2O_2$ (295.9): C, 24.35; H, 1.35; Br, 54.01; N 9.46. Found: C, 24.31; H, 1.39; Br, 54.23; N, 9.61. IR (cm^{-1}): 1725, 1681 (lactam). ^{1}H-nmr (δ [ppm]): 7.22 (s, 1H, CH=Br_2), 7.92 (s, 1H, H-6), 11.35 (s, br, 2H, NH).

5-(Bromoethynyl)-uracil (3)

0.6 g (2 mmol) of **5** were dissolved in 60 ml of abs. DMF and cooled to -10°C. After addition of 0.88 g (8 mmol) of sodium tert.-pentoxide (Aldrich Chemie, Germany; always store under reduced pressure!) the mixture was stirred at -10°C for two hrs. The precipitate was filtered off and dissolved in 20 ml of water. The alkaline solution was neutralized with HCl (15%). The precipitated product was collected by filtration and washed with ice cold water. Yield: 0.41 g (95%). Mp.: >290°C (dec.). Anal. calcd. for $C_6H_3BrN_2O_2$ (215.0): C, 33.51; H, 1.39; Br, 37.16; N, 13.02. Found: C, 33.65; H, 1.30; Br, 37.60; N, 13.20. Ms(70 eV): m/z = 215 (M^+). IR (cm^{-1}): 2207 (ethynyl), 1713, 1658 (lactam). ^{1}H-nmr (δ [ppm]): 7.85 (s, 1H, H-6), 11.35 (s, br, 2H, 2x NH).

5-(Bromoethynyl)-1-[2'-deoxy-3',5'-di-O-(p-chlorobenzoyl)]-uridine (7)

0.43 g (2 mmol) of **5** were refluxed for 4 hrs with 50 ml of HMDS and 0.15 ml chlorotrimethylsilane, a colourless solution resulted thereby. The excess of HMDS was removed by distillation under reduced pressure (20 mbar, 50 - 60°C). The oily residue was dissolved in 50 ml of abs. dichloroethane. To this solution, a mixture of 0.75 g (1.8 mmol) of **6** in 50 ml of dry dichloroethane and 15 mg of $HgBr_2$ as a catalyst were added. After stirring at room temperature for 24 hours, the solvent was evaporated in vacuo and the residue purified via column chromatography (chloroform + methanol = 5 + 1). To achieve a good separation the eluant must flow at a very slow rate, the separation needs 3 days. The product eluting first was the β-isomer.
Yield: 67%. $C_{25}H_{17}BrCl_2N_2O_7$ (608.1).

β-5-(Bromoethynyl)-1-[2'-deoxy-3',5'-di-O-(p-chlorobenzoyl)]-uridine (β-7)

Absolute yield: 0.4 g. Relative yield: 52%. Mp.: 102 - 110°C (dec.). Anal. calcd. for $C_{25}H_{17}BrCl_2N_2O_7$: C, 49.37; H, 2.79; Cl, 11.67; Br, 13.14. Found: C, 49.28; H, 2.81; Cl, 11.49; Br, 13.32. IR (cm^{-1}): 2204 (ethynyl), 1723 - 1638 (lactam, -COO). ^{1}H-nmr (δ [ppm]): 2.65 (m, 2H, H-2',2"), 4.53 (m, 3H, H-4',5',5"), 5.63 (m, 1H, H-3'), 6.27 (t, 1H, H-1', J_{ab} = 6.4 Hz, J_{ac} = 6.8 Hz), 7.52 - 8.29 (m, 9H, H-6, 2x 4-chlorophenyl), 11.76 (s, br, 1H, NH).

α-5-(Bromoethynyl)-1-[2'-deoxy-3',5'-di-O-(p-chlorobenzoyl)]-uridine (α-7)

Absolute yield: 0.37 g. Relative yield: 48%. Mp.: 180 - 185°C (dec.). IR (cm^{-1}): 2202 (ethynyl), 1723 - 1686 (lactam, -COO). ^{1}H-nmr (δ [ppm]): 2.62 (m, 2H, H-2',2"), 4.50 (d, 2H, H-5',5", J = 5.1 Hz), 5.23 (t, 1H, H-4', J = 5.0 Hz), 5.62 (d, 1H, H-3', J = 4.8 Hz), 6.27 (d, 1H, H-1', J = 5.2 Hz), 7.51 - 8.33 (m, 9H, H-6, 2x 4-chlorophenyl), 11.69 (s, br, 1H, NH).

5-(Bromoethynyl)-2'-deoxyuridine (α-8, β-8)

0.15 g (0.25 mmol) of α- resp. β-**7** were dissolved in 2 ml of abs. DMF and diluted with 10 ml of abs. tert.-pentanol. The solution was cooled to 0°C and 0.112 g (1 mmol) of sodium tert.-pentoxide were added. After stirring for 3 hrs at 0°C the solution was neutralized with Amberlite® IR-120 (strongly acidic ion exchange resin). The resin was washed with methanol and the combined solutions were evaporated under reduced pressure. The oily residue was dissolved in ether and stirred at room temperature, until a solid separated. The precipitate was removed by filtration and washed with ether. $C_{11}H_{11}BrN_2O_5$ (331.0).

5-(Bromoethynyl)-β-2'-deoxyuridine (β-8)

Prepared from β-7. Yield: 70 mg (85%). Mp.: 130 - 140°C. Calcd. for $C_{11}H_{11}BrN_2O_5$: C, 39.91; H, 3.32; Br, 24.14; N, 8.45. Found: C, 39.54; H, 3.35; Br, 24.60; N, 8.39. IR (cm^{-1}): 3416 (OH), 2204 (ethynyl), 1693 (lactam). ^{1}H-nmr (δ [ppm]): 2.05 - 2.19 (dd, 2H, H-2',2", J_{ab} = 6.2 Hz, J_{ac} = 6.1 Hz), 3.42 - 3.60 (m, 2H, H-5',5"), 3.79 (1H, H-4'), 4.21 (dd, 1H, H-3'), 5.15 (s, br, 2H, OH), 6.08 (t, 1H, H-1', J = 6.5 Hz), 8.29 (s, 1H, H-6), 11.50 (s, br, 1H, NH).

5-(Bromoethynyl)-α-2'-deoxyuridine (α-8)

Prepared from α-7. Yield: 66 mg (80%). Mp.: 160 - 170°C. IR (cm^{-1}): 3486 (OH), 2204 (ethynyl), 1693 (lactam). ^{1}H-nmr (δ [ppm]): 2.01 (m, 2H, H-2',2"), 3.40 (m, 2H, H-5',5"), 4.20 (m, 2H, H-3',4'), 4.79, 5.31 (2x s, br, 2x 1 H, 2x OH), 6.05 (dd, 1H, H-1'), 8.17 (s, 1H, H-6), 11.58 (s, br, 1H, NH).

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Dedicated to Prof. Dr. H.J. Roth, University of Tübingen, Germany, on the occasion of his 65th birthday

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